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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/869,475	Applicant(s) MORISHITA ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9,11,12,14,48 and 51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9,11,12,14,48 and 51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment filed on 3/28/07 was entered.

Amended claims 9, 11-12, 14, 48 and 51 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The provisional rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-11 of copending Application No. 10/615,262 in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS) was withdrawn in light of Applicant's amendment to claims in the copending Application.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 9, 11-12, 14, 48 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Amended claim 9 and its dependent claims recite the limitation “**administered to the subject once every three to five weeks**”. While the originally filed specification teaches that the therapeutic agent of the invention is suited for administration once every few days or once every few weeks, and once per week is preferred (page 9, lines 32-34), there is **no written support** in the originally filed specification that teaches specifically for administering a hepatocyte growth factor gene to a subject once every three to five weeks in the method as now claimed. Applicants cited experiments 1 and 2 in the specification provided a support for this limitation. However, both experiments 1 and 2 disclose that after 3 weeks and 5 weeks after the initial HGF gene therapy, the perfusion ratio of the ischemic site was measured by laser Doppler imager and the skeletal muscle of the lower limb ischemic site was taken and subjected to ALP staining and blood vessel count, respectively. Nothing in these experiments teaches or suggests that the specific concept of administering a hepatocyte growth factor gene to a subject once every three to five weeks.

Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate specifically or have possession of invention as claimed at the time the application was filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

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the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 9, 11-12, 14, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al. (EP 0 847757 A1; IDS) in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS) and Isner (US 6,121,246; Cited previously). ***This is a new ground of rejection necessitated by Applicant's amendment.***

Morishita et al teaches a medicament comprising a membrane fusion liposome fused to Sendai virus containing a hepatocyte growth factor (HGF) gene, and a method for treating arterial disorders using the same medicament (col. 2, lines 4-19; col. 6, lines 12-33). Morishita et al further teaches that the HGF gene can also be incorporated into an appropriate vector, including a viral vector such as retrovirus, adenovirus, adeno-related virus and others (col. 6, lines 34-47). Morishita et al further discloses that the medicament can be administered through any route appropriate for diseases to be treated or target organs, including subcutaneously, intraarterially, intramuscularly (col.

7, lines 11-19); and that arterial diseases include insufficiency of peripheral circulation, arteriosclerosis, myocardial infarction, peripheral angiostenosis and others since HGF promotes the proliferation of vascular endothelial cells (col. 5, lines 12-34). Morishita et al further teaches that the content of the HGF gene in the medicament may be appropriately varied depending upon diseases to be treated, target organs, patient's age or body weights, etc. However, **it is appropriate to administer a dose of 0.0001 mg to 100 mg, preferably 0.001 mg to 10 mg, and that the dose may be divided into several days or a few months** (col. 7, line 55 continues to line 3 of col. 8).

Morishita et al does not specifically teach a method for treating diabetic lower limb ischemic disease in a subject using a medicament comprising a hepatocyte growth factor (HGF) gene once every three to five weeks.

At about the effective filing date of the present application (10/29/1999), the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis or gangrene by vascular occlusion. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF (see the entire article).

Additionally, Isner already taught a method for treating ischemic tissue in a mammal which comprises injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein, and such tissues include, for example

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muscle, brain, kidney and lung and ischemic diseases include, for example, limb ischemia, cerebral vascular ischemia, renal ischemia, pulmonary ischemia, ischemic cardiomyopathy and myocardial ischemia (see at least the abstract and Summary of the Invention, particularly col. 3, lines 4-35). Isner further taught that typically, the angiogenic protein is only expressed in therapeutic levels for about two days to several weeks, preferably for about 1-2 weeks, and reinjection of the DNA can be utilized to provide additional periods of expression of the angiogenic protein (col. 6, lines 34-38).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Morisita et al. by also administering a medicament comprising a HGF gene at a dose of 0.0001 mg to 100 mg, preferably 0.001 mg to 10 mg, to a subject once every three to five weeks to treat patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion (e.g., intramuscular injection to a muscle around the affected limb of patients) in light of the disclosure of the Japan Financial News Paper dated 12/14/1998 and the teachings of Isner.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion, and that gene therapy using a gene encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars and to avoid amputation of the limb. Moreover, HGF is also noted to have more potent angiogenesis activity and less side

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effects than VEGF. Furthermore, Isner already taught that that typically, the angiogenic protein is only expressed in therapeutic levels for about two days to several weeks, and reinjection of the DNA can be utilized to provide additional periods of expression of the angiogenic protein.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Morishita et al., the Japan Financial News Paper dated 12/14/1998, and Isner; coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

It is also well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicant's arguments related in part to the above rejection in the Amendment filed on 3/28/07 (pages 5-6) have been fully considered, but they are respectfully not found to be persuasive.

Applicant argues basically that Morishita and the Japan Financial Times article do not teach or suggest administration of an HGF gene into skeletal muscle once every 3-5 weeks. Furthermore, with respect to the Stratford-Perricaudet reference used in previous Examiner's rebuttals to Applicant's arguments, Applicants argue that the reference teaches that transgene expression is dependent on the mode of administration and since intramuscular injection taught by Stratford-Perricaudet to be less effective than intravenous injection, therefore it would not be obvious for one skilled in the art to use intramuscular injection to deliver a transgene to a distant affected site and treat target diseases even if the transgene expression lasted 21 days. Additionally, with respect to the Denham et al (J. Gastrointest. Surg. 2:95-101, 1998; IDS) reference cited previously in the Examiner's rebuttals to Applicant's arguments, Applicants argued that undesirable pancreatic inflammation and tissue destruction were observed following intraperitoneal injection of liposomes and plasmid (page 100, col. 1, first full paragraph); and therefore one skilled in the art would conclude that transgene expression depends on target organs and administration routes and that it would not be obvious to one skilled in the art that intramuscular injection could be effective to deliver a transgene to an affected site and treat target diseases without undesirable effects.

Firstly, please note that neither the Stratford-Perricaudet reference nor the Denham et al reference was used in the rejection under 35 U.S.C. 103(a). Their teachings were used to support the examiner's position that a transgene expression in various forms *in vivo* would be expected to last at least for several days or weeks.

Secondly, with respect to the new limitation "administered to the subject once every three to five weeks", **Isner taught clearly that typically, the angiogenic protein is only expressed in therapeutic levels for about two days to several weeks, preferably for about 1-2 weeks, and reinjection of the DNA can be utilized to provide additional periods of expression of the angiogenic protein** (col. 6, lines 34-38). Therefore, it would have been obvious for an ordinary skilled in the art to modify the teachings of Morishita et al and the Japan Financial News Paper by also readministering to a subject having diabetic ischemic disease a hepatocyte growth factor gene once every three to five weeks to provide additional periods of therapeutic expression levels of the angiogenic protein for the treatment in light of the teachings of Isner.

Thirdly, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In *re Dreyfus*, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In *re Waite et al.*, 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In *re Swenson et al.*, 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In *re Scherl*, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. **However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art.** In *re Sola*, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In *re Normann et al.*, 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In *re Irmischer*, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. **More particularly, where**

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the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

Accordingly, amended claims 9, 11-12, 14, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al. in view of the Japan Financial News Paper dated 12/14/1998 and Isner (US 6,121,246) for the reasons set forth above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Amended claims 9, 11, 14 and 48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-4 of U.S.

Patent No. 6,989,374 B1 in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS). ***This is a modified rejection necessitated by Applicant's amendment.***

The instant claims are directed to a method for the treatment of diabetic ischemic disease in a subject, comprising administering a therapeutically effective amount of a hepatocyte growth factor gene to the muscle of an ischemic site, wherein the hepatocyte growth factor gene is administered to the subject once every three to five weeks, thereby treating the diabetic ischemic disease.

Claims 1 and 3-4 of U.S. Patent No. 6,989,374 B1 are drawn to a method for treating a cardiac muscle disorder comprising administering a therapeutically effective amount of a nucleic acid molecule encoding HGF directly to a part of an affected abdominal lateral cardiac muscle or directly into an abdominal lateral cardiac muscle of a mammal using echocardiographic guidance without thoracotomy, wherein the nucleic acid molecule is encapsulated in a Sendai virus-liposome and expresses an HGF protein that reduces fibrosis and/or promoting angiogenesis of the cardiac muscle.

The claims of the present application differ from the claims of the U.S. Patent No. 6,989,374 B1 in reciting specifically a method for the treatment of diabetic ischemic disease, including diabetic ischemic myocardial infarction, and a hepatocyte growth factor gene is administered to a subject once every three to five weeks. It is also noted that in the issued U.S. Patent No. 6,989,374 B1, the term "administering" includes **once every few weeks**; and the "effective amount" includes a range from about 10 to about 400 ug of HGF gene (col. 6, lines 58-62).

At the effective filing date of the present application, the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis obliterans mainly caused by diabetes mellitus. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF and is therefore expected to be applied to myocardial infarction (see the entire article).

Accordingly, it would have been obvious for an ordinary skilled artisan to apply the method of the U.S. Patent No. 6,989,374 B1 to a mammal or a subject having diabetes mellitus, particularly for treating myocardial infarction, in light of the disclosure of the Japan Financial News Paper dated 12/14/1998, and the administration of a hepatocyte growth factor to the treated subject is once every 3 to 5 weeks.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that gene therapy using a gene encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars in a patient having diabetes mellitus. Furthermore, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF, and is therefore expected to be applied to myocardial infarction.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of U.S. Patent No. 6,989,374 B1 and the Japan Financial News Paper dated 12/14/1998, coupled with a high level of skill for an ordinary skilled artisan

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in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Amended claims 9, 11-12, 14, 48 and 51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,248,722 (Cited previously) in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS) and Isner (US 6,121,246; Cited previously). ***This is a new ground of rejection necessitated by Applicant's amendment.***

The instant claims are directed to a method for the treatment of diabetic ischemic disease in a subject, comprising administering a therapeutically effective amount of a hepatocyte growth factor gene to the muscle of an ischemic site, wherein the hepatocyte growth factor gene is administered to the subject once every three to five weeks, thereby treating the diabetic ischemic disease.

Claims 1-4 of U.S. Patent No. 6,248,722 are drawn to a method for treating a disease (including an arterial disease) in a subject for which HGF is effective, comprising administering intramuscularly to the subject an expression vector containing a HGF gene in a therapeutically effective amount.

The claims of the present application differ from the claims of the U.S. Patent No. 6,248,722 in reciting specifically a method for the treatment of diabetic ischemic

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disease, including diabetic ischemic myocardial infarction, and a hepatocyte growth factor gene is administered to a subject once every three to five weeks. It is also noted that in the issued U.S. Patent No. 6,248,722, the term "administering" includes administering a dose of 0.001 mg to 10 mg of HGF gene into several days or a few months (col. 6, lines 48-54).

At about the effective filing date of the present application (10/29/1999), the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis or gangrene by vascular occlusion. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF (see the entire article).

Additionally, Isner already taught a method for treating ischemic tissue in a mammal which comprises injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein, and such tissues include, for example muscle, brain, kidney and lung and ischemic diseases include, for example, limb ischemia, cerebral vascular ischemia, renal ischemia, pulmonary ischemia, ischemic cardiomyopathy and myocardial ischemia (see at least the abstract and Summary of the Invention, particularly col. 3, lines 4-35). Isner further taught that typically, the angiogenic protein is only expressed in therapeutic levels for about two days to several weeks, preferably for about 1-2 weeks, and reinjection of the DNA can be

utilized to provide additional periods of expression of the angiogenic protein (col. 6, lines 34-38).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method in U.S. Patent No. 6,248,722 by also administering a medicament comprising a HGF gene at a dose of 0.0001 mg to 100 mg, preferably 0.001 mg to 10 mg, to a subject once every three to five weeks to treat patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion (e.g., intramuscular injection to a muscle around the affected limb of patients) in light of the disclosure of the Japan Financial News Paper dated 12/14/1998 and the teachings of Isner.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion, and that gene therapy using a gene encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars and to avoid amputation of the limb. Moreover, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF. Furthermore, Isner already taught that typically, the angiogenic protein is only expressed in therapeutic levels for about two days to several weeks, and reinjection of the DNA can be utilized to provide additional periods of expression of the angiogenic protein.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of U.S. Patent No. 6,248,722, the Japan Financial News Paper

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dated 12/14/1998, and Isner; coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Amended claims 9, 11, 14 and 48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-11 of copending Application No. 10/615,292 in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS) and Isner (US 6,121,246; Cited previously).

This is a new ground of rejection necessitated by Applicant's amendment.

The instant claims are directed to a method for the treatment of diabetic ischemic disease in a subject, comprising administering a therapeutically effective amount of a hepatocyte growth factor gene to the muscle of an ischemic site, wherein the hepatocyte growth factor gene is administered to the subject once every three to five weeks, thereby treating the diabetic ischemic disease.

Claims 7-8, 10-11 of copending Application No. 10/615,292 are drawn to a method for treating myocardial infarction in a subject for which HGF is effective, comprising administering by direct injection into heart muscle of a subject a therapeutically effective amount of an expression vector containing a constitutive promoter operably linked to a HGF coding sequence.

The claims of the present application differ from the claims of the copending Application No. 10/615,292 in reciting specifically a method for the treatment of diabetic ischemic disease, including diabetic ischemic myocardial infarction, and a hepatocyte growth factor gene is administered to a subject once every three to five weeks. It is also noted that in the copending Application No. 10/615,292, the term "administering" includes administering a dose of 0.001 mg to 10 mg of HGF gene into several days or a few months (paragraph 39 on page 11).

At the effective filing date of the present application, the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis obliterans mainly caused by diabetes mellitus. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF and is therefore expected to be applied to myocardial infarction (see the entire article).

Additionally, Isner already taught a method for treating ischemic tissue in a mammal which comprises injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein, and such tissues include, for example muscle, brain, kidney and lung and ischemic diseases include, for example, limb ischemia, cerebral vascular ischemia, renal ischemia, pulmonary ischemia, ischemic cardiomyopathy and myocardial ischemia (see at least the abstract and Summary of the Invention, particularly col. 3, lines 4-35). Isner further taught that typically, the

angiogenic protein is only expressed in therapeutic levels for about two days to several weeks, preferably for about 1-2 weeks, and reinjection of the DNA can be utilized to provide additional periods of expression of the angiogenic protein (col. 6, lines 34-38).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method in copending Application No. 10/615,292 by also administering a medicament comprising a HGF gene at a dose of 0.0001 mg to 100 mg, preferably 0.001 mg to 10 mg, to a subject once every three to five weeks to treat patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion (e.g., intramuscular injection to a muscle around the affected limb of patients) in light of the disclosure of the Japan Financial News Paper dated 12/14/1998 and the teachings of Isner.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion, and that gene therapy using a gene encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars and to avoid amputation of the limb. Moreover, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF. Furthermore, Isner already taught that that typically, the angiogenic protein is only expressed in therapeutic levels for about two days to several weeks, and reinjection of the DNA can be utilized to provide additional periods of expression of the angiogenic protein.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of copending Application No. 10/615,292, the Japan Financial News Paper dated 12/14/1998, and Isner; coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection.

Response to Argument

In the Amendment filed on 3/28/07 (page 6), Applicants simply disagreed with the above rejections on grounds of non-statutory obviousness-type double patenting for the same reasons traverse for the above rejection under 35 U.S.C. 103(a).

Please refer to the same examiner's rebuttals to Applicants' arguments above.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Art Unit: 1633

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D.
PRIMARY EXAMINER